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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/632,149	08/03/2000	R. Andrew Cuthbertson	A-59553-2/DAV/JJD	1941

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/632,149	**Applicant(s)** CUTHBERTSON, R. ANDREW
	Examiner Quang Nguyen, Ph.D.	**Art Unit** 1633

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 July 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *7/11/05*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *23-27*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DAVID GUZO
PRIMARY EXAMINER

8.0-3

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments are respectfully not found persuasive.

1. Apart from the previously presented arguments, Applicant further argue that compared to other tissues, the eye is an easily accessible target for gene therapy, and gene transfer and transgene expression in ocular tissues can be observed and monitored directly. Applicant also asserts that one of skill in the art would reasonably expect transduced ocular cells to express transgene at a therapeutically useful level by citing numerous post-filing publications that demonstrate the attainment of therapeutic effects in the eye via gene therapy. Applicant further argues that the instant specification teaches a similar dosage as that taught in the study of Bennett et al. in which therapeutic effects were obtained, and therefore therapeutically useful expression of a nucleic acid in transfected ocular cells would be expected.

Please note that it is not a straight-forward issue of simply expressing any exogenous gene in any ocular cell population. It is whether an effective or appropriate level of a therapeutic protein could be produced by an appropriate ocular cell population to yield the desired therapeutic effects. This is a major limitation that renders the attainment of any therapeutic effect via gene therapy unpredictable. The various therapeutic effects that are reported by numerous post-filing publications would not reasonably be extrapolated to the specification as filed because there is no evidence that the instant disclosure teaches the same method steps and the same starting materials as those of post-filing publications. For example, where is in the specification as filed that teaches the recobminant adenoviral vector used in the study of Bennett et al? Also please refer to the examiner's response in the Final Office action mailed on 1/11/05 (pages 11-12).

2. On the issue of growth factors other than TGF-beta, Applicant argues that other growth factor polypeptides such as EGF, FGF, KGF and mesodermal gowth factor have been shown to enhance healing of ocular wounds, and therefore one of skill in the art would have been able to use a nucleic acid encoding any of these growth factors in the methods of the presently claimed invention without undue experimentation.

Once again, it is not a straight-forward issue of simply expressing any exogenous gene in any ocular cell population. It is whether an effective or appropriate level of a therapeutic protein could be produced by an appropriate ocular cell population to yield the desired therapeutic effects. It is interesting to note that the instant specification fails to disclose any relevant exogenous nucleic acid encoding any of these growth factors for the methods as claimed, particularly because these are critical materials for the claimed invention.

3. With respect to the Cordeiro article, Applicant argues that topical application and intraocular injection methods for healing ocular wounds with growth factor polypeptides were known and therefore one of ordinary skill in the art would have been able to modulate the wound healing proces without undue experimentation.

Please note that none of the wound healing methods cited by Applicant is remotely related to gene therapy.

4. With respect to the issue on the control expression of TGF-beta in ocular cells, Applicant argues that whether scarring or degeneration is or is not a side effect of the claimed treatment methods is not relevant to the enablement requirement. Applicant further argues that the concentrations of TGF-beta 2 in the range of 330-1330 ng that promote flattening of macular holes do not induce excessive fibrosis or proliferative vitreoretinopathy.

It is noted that there is nowhere in the specification that teaches expression of encoded TGF-beta or any other encoded growth factor polypeptides within a therapeutic range has been attained? There is also no written support in the specification as filed that Applicant contemplates specifically the use of TGF-beta 2 in the methods as claimed.